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(54) Title: 1,2-DIHYDRO-8-PIPERAZINYL-4-PHENYLIMIDAZOPYRIDOPYRAZINE OXIDES AND 1,2-DIHYDRO-8-PIPERAZINYL-4 PHENYLIMIDAZOQUINOXALINE OXIDES USEFUL FOR TREATING TUMORS

(57) Abstract

1,2-Dihydro-8-piperazinyl-4-phenylimidazopyridopyrazine oxides and 1,2-dihydro-8-piperazinyl-4-phenylimidazo quinoxaline oxides are useful in the treatment of cancer and in particular in the treatment of hypoxic tumours.

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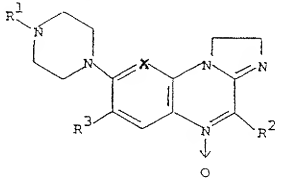
1,2-DIHYDRO-8-PIPERAZINYL-4-PHENYLIMIDAZOPYRIDORYRAZINE OXIDES AND 1,2-DIHYDRO -8-PIPERAZINYL-4 PHENYLIMIDAZOQUINOXALINE OXIDES USEFUL FOR TREATING TUMORS

The present invention relates to the use of dihydroimidazo-quinoxalines and dihydroimidazo-pyridopyrazines in the manufacture of medicaments useful in the treatment of cancer.

EP-A-214,632 discloses quinoxaline and pyridopyrazine derivatives which are useful as anti-anaerobic agents, for the treatment of diseases related to anaerobic bacteria. Such diseases include for example, post-operative sepsis following lower gastrointestinal surgery or female urinogenital surgery, pelvic inflammatory disease, ulcers, gangrene, trichomonal vaginitis, non-specific vaginitis, amoerbiasis, giardiasis, periodontal disease, acne, and the like.

Accordingly the present invention provides the use in the manufacture of a medicament, for use in the treatment of a tumour, such as a hypoxic tumour, of a compound of formula (I)



(I)

wherein R^1 is alkyl of 1 to 6 carbon atoms, benzyl, phenyl,

$(R^4 - \overset{\overset{O}{\|}}{S}\overset{\overset{O}{\|}}{}) -$ where R^4 is alkyl of 1 to 6 carbon atoms,

$(NH_2 - \overset{\overset{O}{\|}}{C} - CH_2) -$,

$(R^5 - \overset{\overset{O}{\|}}{C}) -$ where R^5 is alkyl of 1 to 6 carbon atoms, aminomethyl, pyridinyl, phenyl, halophenyl (e.g. fluorophenyl, chlorophenyl or bromophenyl) or

$(R^6 - O - \overset{\overset{O}{\|}}{C} - NHCH_2) -$ where R^6 is alkyl of 1 to 6 carbon atoms; R^2 is phenyl unsubstituted or substituted by 1 or 2 substituents selected from halogen and alkoxy of 1 to 6 carbon atoms;

R^3 is hydrogen or halogen; and

X is -CH= or -N=; or

a pharmaceutically acceptable salt thereof.

According to a further feature the present invention provides a method for the treatment of a human or animal patient suffering from a tumour, such as a hypoxic tumour, which method comprises administering to the patient an effective amount of a compound of Formula (I), as hereinbefore defined, or a pharmaceutically acceptable salt thereof.

The invention provides, as a further feature, products comprising a compound of Formula (I) as hereinbefore defined or a pharmaceutically acceptable salt thereof, for use in the treatment of a tumour, such as a hypoxic tumour.

The invention provides, as yet a further feature, a pharmaceutical agent for use in the treatment of a tumour, such as a hypoxic tumour, which agent comprises a compound of Formula (I), as hereinbefore defined, or a pharmaceutically acceptable salt thereof.

In the compounds of formula (I), the alkyl and alkoxy groups may be either straight or branched.

It is preferred that any alkyl groups in the compounds of formula (I) (including alkyl groups which form part of alkoxy groups) be alkyl groups of 1 to 4 carbon atoms, i.e. methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl. Particularly preferred alkyl substituents are methyl, and ethyl, most preferably methyl.

Compounds of formula (I) in which R^2 is substituted phenyl may be substituted in any position by 1 or 2 substituents selected from halogen atoms, e.g. fluorine, chlorine or bromine atoms, and alkoxy groups e.g. methoxy or ethoxy. The following substituted phenyl groups are illustrative of such groups: 4-chlorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 3-bromophenyl, 3-chlorophenyl, 2-methoxyphenyl, 4-methoxyphenyl, 3-

methoxyphenyl, 2-ethoxyphenyl, 4-ethoxyphenyl, 3-ethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,4-diethoxyphenyl 3,5-diethoxyphenyl and 2-chloro-4-methoxyphenyl. Preferred substituted phenyl groups are 4-halophenyl groups, such as 4-fluorophenyl.

Where R^1 is a group $R^5-\overset{O}{\overset{\|}{C}}-$, preferably R^5 is aminomethyl, pyridinyl, phenyl or halophenyl.

Preferred compounds of formula (I) are those in which R^1 is alkyl of 1 to 6 carbon atoms, benzyl or phenyl, especially those in which R^1 is alkyl of 1 to 6 carbon atoms.

Also preferred are compounds of formula (I) in which R^2 is unsubstituted phenyl or in which R^3 is hydrogen. Preferably X is -N=.

Of the compounds of formula (I) 1,2-dihydro-8-(4-methylpiperazinyl)-4-phenylimidazo[1,2-a]-quinoxaline-5-oxide and 1,2-dihydro-8-(4-methylpiperazinyl)-4-phenylimidazo[1,2-a]pyrido[3,2-e]pyrazine-5-oxide may be specifically mentioned as particularly preferred. Of these two the pyrido-pyrazine is more preferable.

Salts of the compounds of formula (I) used in the present invention may be any pharmaceutically acceptable acid addition salts. Examples of suitable salts include, salts of inorganic acids such as chlorides, bromides, iodides, phosphates and sulphates and salts of organic acids such as

acetates, citrates, lactates and tartrates.

The compounds used in the present invention are known compounds which may be prepared using known methods. In particular they may be prepared according to procedures described in EP-A-214,632.

The compounds of Formula (I) may according to the invention, be used in uncomplexed form or in the form of a complex, such as a complex formed with one or more molecules of organic solvent, water (i.e. a hydrate), or hydrogen halide, e.g. hydrogen chloride.

The compounds of formula (I) are useful in increasing the sensitivity of tumour cells to radiation in radiotherapy and as bioreductive agents. A compound is administered to a patient having a radiation-treatable cancer, prior to or after, more typically shortly after irradiation of the tumour, in an amount effective to increase the sensitivity of the tumour cells to the effects of the irradiation.

Any solid tumour, which may have regions where cells are radiobiologically hypoxic and become resistant to ionising radiation, may be treated. Examples of such tumours are epithelial tumours of the head, neck, thorax and abdomen, soft tissue sarcomas and brain tumours. The compounds of formula (I) can therefore be employed in the radiotherapy of all such solid tumours where hypoxic cells are known or suspected to exist.

The compounds of formula (I) may also be used where an agent having differential hypoxic cytotoxicity is required. The compounds can be employed for chemopotentiation of a chemotherapeutic agent or as a chemotherapeutic by administration of a compound (I) to a patient having a localised or metastatic cancer. Administration is carried out prior to simultaneously with or after administration, typically prior to or simultaneously with, of a chemotherapeutic agent such as melphalan, cyclophosphamide, 5-fluorouracil, adriamycin, CCNU(1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) or tumour necrosis factor (TNF). Any solid tumours, such as above, which are primary or secondary deposits, where it is known or suspected that hypoxic cells are present can therefore benefit from treatment employing a compound of formula (I).

The compounds of formula (I) are useful in particular for the treatment of hypoxic tumours. However the compounds of formula (I) may also be useful in the treatment of other tumours rich in enzymes required to activate the compounds of formula (I) as bioreductive agents or radiosensitisers. Such enzymes may include cytochrome P450, NADPH dependent cytochrome P450 reductase, DT-diaphorase and xanthine oxidase.

The compounds of formula (I) and salts thereof may be administered orally or intravenously. The amount administered depends on factors such as the cancer, the

condition of the patient and the body weight of the patient. Typically, however, doses of 50 to 1000mg/m^2 of a patient's body area may be employed.

A compound of formula (I) may be formulated in a manner appropriate to the treatment for which it is to be used by bringing it into association with a pharmaceutically compatible carrier or diluent. The compound may be included in a dosage form suitable for bolus injection or such as a tablet or capsule, for example a capsule comprising known formulation components. The compound may also be formulated for intravenous administration e.g. in a saline drip solution.

The following Examples illustrate the invention.

EXAMPLE 1

C3H mice in which the KHT tumour had been implanted subcutaneously were administered RB 90003X [1,2-dihydro-8-(4-methylpiperazinyl)-4-phenylimidazo-[1,2a]-pyrido-[3,2-e]pyrazine-5-oxide] interperitoneally immediately after irradiation with 10 Gy X-rays. The results are set out in Table 1 and comparison is made with the anti-tumour effects of the benztriazene di-N-oxide, SR 4233 [3-amino-1,2,4-benzotriazine 1,4-dioxide]; the dual function nitroimidazoles RSU 1069 [1-(2-nitro-1-imidazolyl)- 3-(1-aziridino)-2-propanol] and RB 6145 [1-(2-nitro-1-imidazolyl)-3-(2-

bromoethylamino)-2-propanol] and the radiosensitizer misonidazole. Values of the maximum tolerated dose (MTD) to C3H mice are also recorded. All compounds were administered in phosphate buffered saline (PBS) at pH 7.4, except RB 6145 which was in PBS at pH 5.4. Results are expressed as the administered i.p. dose required to cause a 4-fold increase in cell killing compared to radiation alone, i.e. 10 Gy alone gives a tumour cell surviving fraction of 2×10^{-2}

TABLE 1

Compound	Administered dose required to give a surviving fraction of 5×10^{-3}	MTD
	(μmol kg^{-1})	
RB 90003X	80	330
SR 4233	150	400
RSU 1069	90	380
RB 6145	200	940
Misonidazole	5000	5000

Clearly the anti-tumour efficacy of RB 90003X is similar to that of the other bioreductive drugs RSU 1069 and SR 4233.

EXAMPLE 2

C3H mice in which the transplantable rodent tumour RIF-1 had been implanted subcutaneously were administered RB 90003X intraperitoneally immediately after irradiation with 10 Gy X-rays. The time for the tumour to increase in size to four times its original volume is compared with the corresponding time where no treatment was applied to the tumour and where the tumour was treated by irradiation alone.

The results shown in Table 2 below indicate that the use of RB 90003X immediately after irradiation to kill of viable cells which were hypoxic at the time of irradiation, leads to a significant slowing in the growth of the tumour.

TABLE 2

Treatment	Time (in days) to 4 x treatment volume
None	5.0
25 Gy only	24
30 Gy only	35
25 Gy + 100 mg/kg RB 90003X	36
25 Gy + 50 mg/mg RB 90003X	43
25 Gy + 20 mg/kg RB 90003X	41

EXAMPLE 3

The toxicity of RB 90003X towards aerobic or hypoxic V79 Chinese hamster cells in vitro is shown in Table 3 and comparison is made with SR 4233. Toxicity was determined by the use of the modified MTT assay (Stratford and Stephens (1989), Int. J. Radiat. Oncol. Biol. Phys. 16, 973-976). Values quoted represent concentrations of drug required to reduce proliferation of treated cultures by 50%. Cells are treated with various drug doses for 3 hours at 37°C under aerobic or hypoxic conditions, following drug removal cells are allowed to proliferate for 3 days prior to assay.

TABLE 3

Compound	C air	C N_2	Ratio
	mmol dm^{-3}		
RB 90003X	1.0	0.05	20
SR 4233	0.3	0.006	50

Clearly RB 90003 X is substantially more toxic to hypoxic compared with aerobic cells. While the differential is slightly higher for SR 4233, the aerobic toxicity of the mono-N-oxide is considerably less.

As a result of further determinations of the toxicity of RB 90003X using the same method, the following cumulative results were obtained:-

C air	C N_2	Ratio
0.85	0.07	12.1

EXAMPLE 4

The procedure of Example 3 was repeated but using a cells from a variety of human tumour cell lines, rather than the V79 Chinese hamster cells. The results were as follows:-

TABLE 4

Cell line	C air	C N_2	Ratio
H647 - lung tumour	1.8	0.15	12
H322 lung tumour	1.3	0.37	3.5
H460 lung tumour	2.8	0.15	18
A549 lung tumour	2.6	0.18	14
HT29 - colon tumour	1.2	0.07	17
MDA468 - breast tumour	1.3	0.07	19

EXAMPLE 5

The procedure of Example 3 was repeated but using a variety of compounds of Formula (I) rather than RB 90003X.

The results were as follows:-

TABLE 5

Compound	C air	C $(N)_2$	Ratio
RB 91726	0.9	0.023	42.0
RB 91701	0.63	0.055	11.5
RB 92810	0.8	0.03	26
RB 92812	1.0	0.04	25

The compounds identified in Table 4 are as follows:-

RB91726 - 1,2-Dihydro-8-(4-methylpiperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide bishydrochloride

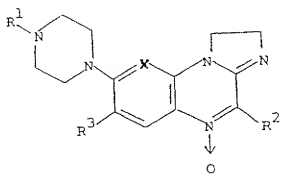
RB91701 - 1,2-Dihydro-8-(4-methylpiperazinyl)-4-phenylimidazo [1,2-a] quinoxaline 5-oxide

RB92810 - 1,2-Dihydro-8-(4-methylpiperazinyl)-4(p-fluorophenyl)imidazo-[1,2-a] pyrido [3,2-e] pyrazine 5-oxide bishydrochloride

RB92812 - 1,2-Dihydro-8-(4-ethylpiperazinyl)-4-phenylimidazo [1,2-a] pyrido [3,2-e] pyrazine 5-oxide

CLAIMS

1. Use in the manufacture of a medicament, for use in the treatment of a tumour, of a compound of formula (I)



(I)

where R^1 is alkyl of 1 to 6 carbon atoms, benzyl, phenyl,

$(R^4 - \overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}) -$ where R^4 is alkyl of 1 to 6 carbon atoms,

$(NH_2- \overset{\overset{O}{\|}}{C} - CH_2)-$,

$(R^5 - \overset{\overset{O}{\|}}{C})-$ where R^5 is alkyl of 1 to 6 carbon atoms, aminomethyl, pyridinyl, phenyl, halophenyl or

$(R^6- O - \overset{\overset{O}{\|}}{C} - NHCH_3)-$ where R^6 is alkyl of 1 to 6 carbon atoms;

R^2 is phenyl unsubstituted or substituted by 1 or 2 substituents selected from halogen and alkoxy of 1 to 6 carbon atoms;

R^3 is hydrogen or halogen; and

X is -CH= or -N=; or

a pharmaceutically acceptable salt thereof.

2. Use according to claim 1 of a compound of formula (I) in which R^1 is alkyl of 1 to 6 carbon atoms, benzyl or phenyl, or a pharmaceutically acceptable salt thereof.

3. Use according to claim 3 in which R^1 is alkyl of 1 to 6 carbons atoms, or a pharmaceutically acceptable salt thereof.

4. Use according to claim 3 in which R^1 is methyl or ethyl, or a pharmaceutically acceptable salt thereof.

5. Use according to any one of claims 1 to 4 of a compound of formula (I) in which R^2 is unsubstituted phenyl or 4-halophenyl, or a pharmaceutically acceptable salt thereof.

6. Use according to any one of claims 1 to 5 of a compound of formula (I) in which R^3 is hydrogen, or a pharmaceutically acceptable salt thereof.

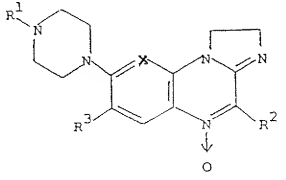
7. Use according to any one of claims 1 to 6 of a compound of formula (I) in which X is -N=, or a pharmaceutically acceptable salt thereof.

8. Use according to claim 1 of 1,2-dihydro-8-(4-methylpiperazinyl)-4-phenylimidazo[1,2-a]quinoxaline-5-oxide or 1,2-dihydro-8-(4-methylpiperazinyl)-4-phenylimidazo[1,2-a]pyrido[3,2-e]pyrazine-5-oxide, or a pharmaceutically acceptable salt thereof.

9. Use according to claim 8 of 1,2-dihydro-8-(4-methylpiperazinyl)-4-phenylimidazo[1,2-a]pyrido[3,2-e]pyrazine-5-oxide, or a pharmaceutically acceptable salt thereof.

10. Use according to any one of the preceding claims for use in the treatment of a hypoxic tumour.

11. A method for the treatment of a human or animal patient suffering from a tumour which method comprises administering to the patient an effective amount of a compound of formula (I)



(I)

where R^1 is alkyl of 1 to 6 carbon atoms, benzyl, phenyl,

$(R^4 - \overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}) -$ where R^4 is alkyl of 1 to 6 carbon atoms,

$(NH_2- \overset{\overset{O}{\|}}{C} - CH_2)-$,

$(R^5 - \overset{\overset{O}{\|}}{C})-$ where R^5 is alkyl of 1 to 6 carbon atoms, aminomethyl, pyridinyl, phenyl, halophenyl or

$(R^6- O - \overset{\overset{O}{\|}}{C} - NHCH_2)-$ where R^6 is alkyl of 1 to 6 carbon atoms;

R^2 is phenyl unsubstituted or substituted by 1 or 2 substituents selected from halogen and alkoxy of 1 to 6 carbon atoms;

R^3 is hydrogen or halogen; and

X is -CH= or -N=; or

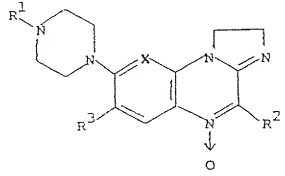
a pharmaceutically acceptable salt thereof.

12. A method according to claim 11 for the treatment of a patient having a solid tumour in which it is known or suspected that hypoxic cells are present.

13. A method according to claim 11 or 12, in which the tumour is a radiation-treatable cancer, the compound of formula (I) is administered to increase the sensitivity of the tumour to the effects of irradiation, and the tumour is then irradiated, the compound of formula (I) being administered prior to or after irradiation of the tumour.

14. A method according to claim 11 or 12, wherein the compound of formula (I) is administered for chemopotentiation of a chemotherapeutic agent and the chemotherapeutic agent is administered prior to, after or simultaneously with the compound of formula (I).

15. Products, for use in the treatment of a tumour, comprising a compound of Formula (I)



(I)

where R^1 is alkyl of 1 to 6 carbon atoms, benzyl, phenyl,

$(R^4 - \overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}) -$ where R^4 is alkyl of 1 to 6 carbon atoms,

$(NH_2- \overset{\overset{O}{\|}}{C} - CH_2) -$,

$(R^5 - \overset{\overset{O}{\|}}{C}) -$ where R^5 is alkyl of 1 to 6 carbon atoms, aminomethyl, pyridinyl, phenyl, halophenyl or

$(R^6- O - \overset{\overset{O}{\|}}{C} - NHCH_2) -$ where R^6 is alkyl of 1 to 6 carbon atoms;

R^2 is phenyl unsubstituted or substituted by 1 or 2 substituents selected from halogen and alkoxy of 1 to 6 carbon atoms;

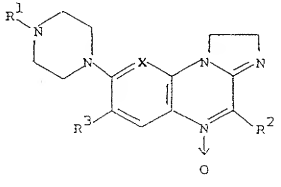
R^3 is hydrogen or halogen; and

X is -CH= or -N=; or

a pharmaceutically acceptable salt thereof.

16. Products according to claim 15 for use in the treatment of a hypoxic tumour.

17. A pharmaceutical agent for use in the treatment of a tumour, which agent comprises a compound of Formula (I)



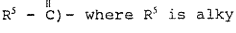
(I)

where R^1 is alkyl of 1 to 6 carbon atoms, benzyl, phenyl,

where R^4 is alkyl of 1 to 6 carbon atoms,

where R^5 is alkyl of 1 to 6 carbon atoms,

aminomethyl, pyridinyl, phenyl, halophenyl or



where R^6 is alkyl of 1 to 6 carbon atoms;

R^2 is phenyl unsubstituted or substituted by 1 or 2 substituents selected from halogen and alkoxy of 1 to 6 carbon atoms;

R^3 is hydrogen or halogen; and

X is -CH= or -N=; or

a pharmaceutically acceptable salt thereof.

18. An agent according to claim 17 for use in the treatment of a hypoxic tumour.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/495

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0214632 (G.D. SEARLE & CO.) 18 March 1987, see abstract; examples 20-22; claims (cited in the application)	1-14
X	---	15-18
A	Chemical Abstracts, vol. 101, no. 7, 13 August 1984, (Columbus, Ohio, US), P.C. PARTHASARATHY et al.: "Heterocyclic N-oxides: Part I - Syntheses of 1,2-dihydroimidazo[1,2-a]quinoxaline 5-oxides and 2,3-dihydro-1H-pyrimido[1,2-a]quinoxaline 6-oxides and their antiprotozoal activity", see page 618, abstract no. 55038c, & INDIAN J. CHEM., SECT. B. 1983, 22B(12), 1250-1, see abstract	1-18
	--- -/-	

* Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04-09-1992	29. 10. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	WO,A,9007496 (SLOAN-KETTERING INSTITUTE FOR CANCER RES.) 12 July 1990, see abstract; page 1, line 10 - page 2, line 25; claims 1-5 ---	1-18
A	J. Org. Chem., vol. 43, no. 10, 1978, American Chemical Society; M.J. STRAUSS et al.: "Annelations of amidines on halonitroaromatics. A one-step route to quinoxaline and imidazoquinoxaline N-oxides and related structures", pages 2041-2044, see whole document -----	1-18

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

ALTHOUGH CLAIMS 11-14 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN/ ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 9201203 SA 61410

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 22/10/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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